REMARKS

Priority

Applicants respectfully disagree with the allegations regarding priority in the Office Action. Nevertheless, a reference to the prior filed international application is provided it the specification herewith as requested by the Examiner.

Information Disclosure Statement

The Examiner did not consider the previously filed IDS at all, which at least to the extent of the US patent application references should have by considered. Accordingly, the consideration of at least said US patent references is respectfully requested.

For the record applicants note that each foreign patent reference cited in the IDS has a US family member thereof cited in the IDS. Thus, the consideration of the US family member patent application publications in effect also satisfies the consideration of the corresponding foreign patent references.

The First Rejections Under 35 USC § 112, first paragraph

The Office Action rejects solvates and derivatives of the compounds of formula I as allegedly not enabled.

These terms have been deleted from the previously pending claims, but new claims are added containing the term solvate and more specific embodiments of solvates, and more specific embodiments of derivatives, e.g., prodrugs. Thus, the following comments are provided.

Regarding solvates and hydrates, the Office Action quotes a passage from *Vippagunta* which indicates that certain predictions about the form of solvates or hydrates of a compound are complex and difficult.

However, the Office Action appears to ignore or disregard the relevance of numerous passages within the same document, which provide support for the claims being enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether 1, 2 or 3 ½, etc. solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates, including mono- and di-hydrates, and alcoholates, including addition compound of a compound of formula I with methanol or ethanol, and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above-discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success for forming solvates or hydrates. While certain predictions may be difficult in the art of forming solvates (e.g., the exact form of a solvate), the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely. The proper question under patent law is not what the Office Action poses, i.e., the predictability of "which solvates or hydrates" would form, but rather whether the formation of "solvates or hydrates" is predictable.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

The Office Action also cites *Byrn*, which allegedly teaches that the formation of solvates is by no means universal among drug substances. However, that does not mean at all

that the formation of solvates is not enabled. One of ordinary skill in the art knows that not all drug compounds form solvates, but that many do, and would thus account for such lack of universal behavior, which is not required under patent law for an invention to be enabled.

Moreover, *Byrn*, just as *Vippagunta*, rather than supporting the position of the Office Action, supports the conclusion that enablement indeed is present in the current situation. A large amount of science is discussed, providing guidance to the preparation of solvates, e.g., providing conditions, general structural considerations, stability issues, effects of humidity, etc., while teaching even in the passage quoted by the Office Action that hydrated or solvated crystal forms are "widespread."

The Office Action also alleges that *Byrn* teaches that the behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration. This allegation is baseless and also irrelevant. Nothing in the record indicates that the behavior of certain compounds from a list of compounds prepared nearly four decades ago in 1971 undergoing dehydration and/or melting has any relevance to the presently claimed invention. For example, the conditions of dehydration and melting are not relevant to the presently claimed invention. Additionally, the teaching in *Byrn* is that the compounds from said list when undergoing dehydration prior to melting "show unusual behavior." Nothing about the predictability of said "unusual behavior" is taught or mentioned.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case.

In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates or hydrates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). As such, there is

no basis for the rejection.

In *Marzocchi*, the court stated that

> In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. (Emphasis added.)

Nothing in the record of the present case provides basis for doubt, and the USTPO has not provided any evidence substantiating any such doubts. No relevant statements in the application are contrary to generally accepted scientific principles on their face. To the contrary, even the alleged evidence cited in support of the rejection teaches that "one-third of the pharmaceutically active substances are capable of forming crystalline hydrates," or that the formation thereof is "widespread," etc.

The Office Action also alleges that applicants did not exemplify any solvates. However, there is no requirement for examples at all in patent applications. See, for example, *In re Marzocchi*, 169 U.S.P.Q. 367 (1971), stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." (Emphasis added.) The MPEP in agreement with this by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." (Emphasis added.) See MPEP § 2164.02.

The Office Action also alleges that the properties of the solvates and hydrates, e.g., *in vivo* activity, may be different than of the parent compound. No unpredictability regarding activity is taught or suggested by the cited art, and nor is such teaching therein is alleged. Instead, one of ordinary skill in the art would know that different forms may have differences

in activity, and such artisan can account for such differences, and test for such differences by using routine testing techniques. Merely there having a possibility of differences in activity generally among different forms of a compound, does not mean at all that the therapeutic activity thereof is unpredictable. If such were the case, the use of solvates and hydrates in the pharmaceutical art would not be as widespread and common as taught by the cited art of record.

Moreover, even in an unpredictable art, which is not the situation in the present case regarding chemical preparations, there is no requirement that an applicant provide examples directed to the preparation of each and every species of a claimed invention. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

Despite all the above, applicants provide further information clearly demonstrating that solvate formation, for example, of mono- or di-hydrate or various specific alcoholates, is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-233 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to

what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the mono- or di-hydrate or alcoholate of a specific compound of the present claims.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take the finite number of compounds of the claimed invention, bring them together with various solvents, i.e., water or various alcohols, etc., and check whether, e.g., a mono- or di-hydrate or addition compound with methanol, etc., has formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Regarding prodrugs, the Office Action makes various allegations related to the eventual development of candidates, toxicity, poor pharmacokinetic properties, lack of reliable high-throughput computer modeling, (see, e.g., the middle of page 6), and effectiveness in clinical trials (see, e.g., top of page 8).

However, all these issues are down the line normally in the art of pharmaceuticals from the time of patenting as explicitly recognized by the Federal Circuit, in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stating that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Regarding the enablement of prodrugs, e.g., of the claimed compounds modified with, e.g., an alkyl or acyl group, or with a sugar or oligopeptide, one of ordinary skill in the art knows how to prepare such compounds (e.g., by binding a sugar to the compound of formula I, e.g., through a metabolically labile bond (which are well known in the art), which bond is metabolized once administered to a subject), and can, through routine experimentation, determine whether the metabolite formed would be a compound of the present claims, e.g., by routine testing for the presence of the compound of the claims, e.g., in a sample taken from the subject.

Reconsideration is respectfully requested.

The Second Rejections Under 35 USC § 112, first paragraph

The Office Action rejects compounds as allegedly not enabled that do not have the specific substituents listed in the top part of page 9 of the Office Action. The Office Action also alleges that applicants have not provided any data suggesting that any molecule other than the small, disclosed subset of compounds (29 examples) would be effective raf kinase inhibitors.

There is no basis for this rejection and no basis for requiring further data. The Office Action places the cart before the horse. The courts have placed the burden upon the USPTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. Only after this burden has been met, does the burden shift to applicants, e.g., to provide further evidence.

The disclosure "*must* be taken as in compliance with the enabling requirement of the

first paragraph of § 112 unless there is reason to doubt the objective truth of the statement contained therein, which must be relied on for enabling support." (Emphasis added.) See *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). No such evidence or reason for doubting Applicants' disclosure is provided.

The specification provides ample guidance on how the claimed compounds are prepared, i.e., general teachings (see, e.g., pages 23-26) as well as specific reaction schemes (see, e.g., pages 46-49) to achieve the claimed compound, as well as specific examples (see, e.g., pages 50-56) are provided, in addition to citing reference(s) (see, e.g. page 26) that teach the preparation of the claimed compounds, and providing examples (assays) of how to test the compounds for activity (see, e.g., pages 56-61).

Additionally, "the [enablement] requirement is satisfied if, given what they [those of ordinary skill in the art] already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003). Making the compounds of the claimed invention would be routine for those of ordinary skill in the art since they are prepared analogously to known processes as taught by the specification (see, e.g., pages 24 and 26). See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art"); *In re Howarth,* 654 F.2d at 105, 210 USPQ 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); *In re Gay*, 309 F.2d 769, 774, 135 USPQ 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.")

Explicitly providing examples for preparing species having each possible substituent is not necessary to enable the full scope of the claims. There is no such requirement imposed by law. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

Instead, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also states that "compliance with the

enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on the bare allegation that the disclosure does not provide enablement to all of the claimed compounds. No evidence has been presented which would demonstrate that the guidance provided by the specification or what is already known in the art is inadequate to enable, e.g., the preparation of the claimed compounds without undue experimentation. In light of the disclosure, taken in combination with knowledge possessed by one of ordinary skill in the art, sufficient guidance is provided to objectively enable one of ordinary skill in the art to make and use the claimed invention using no more than routine experimentation.

Moreover, the court in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) held that the test for enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In view of the teachings in combination with the state of the prior art, there is no basis for rejection herein.

Nevertheless, applicants address the remaining specific allegations from the Office Action also.

The rejection has the underlying premise, allegation, that the "pharmaceutical art is unpredictable," citing *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) in support. However, there is no basis for such an allegation or conclusion. Fisher does not stand for the proposition that the pharmaceutical art is unpredictable *per se*. The court in *Fisher* stated that "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." Thus, merely concluding that the pharmaceutical art is unpredictable without looking at the factors involved is an improper basis for the allegation.

Additionally, with respect to *Fisher*, the court held therein that the appellant, who was the first to achieve a potency of greater than 1.0 for adrenocorticotrophic hormones ("ACTHs"), had not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of "at least 1" rendered the claims insufficiently

supported under the first paragraph of 35 U.S.C. §112. Thus, the situation and question considered by the court in *Fisher* is very different than the one present case. The applicant therein was the "first" to achieve a potency of greater than 1.0, but not greater than 2.3, while the claims were directed with an open end to a potency of "at least 1." In the present case, other compounds are already known to treat conditions claimed, and the claims are not open ended.

Instead of requiring a vast amount of data, The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

The Office Action also alleges that the preface of a book by *Dorwald* teaches that "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are ..." This material is completely irrelevant to patent law. As discussed-above, patents directed to chemicals, e.g., pharmaceuticals, are not written to non-chemists. See *In re Howarth,* 654 F.2d at 105, 210 USPQ 689 (CCPA 1981). ("An inventor need not ... explain every detail since he is speaking to those skilled in the art.") Additionally, the inefficiency of "research" chemists is also irrelevant. The claims here are directed to compounds whose synthesis methods have been taught in the application, which methods can be followed by those of ordinary skill (who are not necessarily inefficient research chemists).

The Office Action also alleges that "as demonstrated by Dumas, et al., and Brown and Brown, similar compounds inhibit distinct unrelated enzymes." See Office Action at top of page 10. The Office Action also alleges in the middle of page 11 that "Brown and Brown demonstrate that related compounds inhibit a different kinase (p38)." First, the Office Action offers no explanation of the alleged "similar" relationship. Moreover, Dumas et al. involved the enzyme raf kinase. See title. Therefore, the rejections are moot for the reasons discussed above.

Reconsideration of the rejection is respectfully requested.

Election/Restriction

Applicants respectfully continue to disagree with the restriction requirement for reasons of record.

Please consider the following additional comments regarding withdrawn claims 12, 13, 14 and 31, which claims are directed to products comprising the compound product of the elected group.

If the elected compound products themselves are patentable, products comprising the same compound products should be patentable as well, as the consideration thereof should only be of minimal effort to the USPTO.

Furthermore, the articles of product claims 12, 13, 14 and 31 are combinations of the compound products of the elected claims and other components. As such, it is respectfully submitted that the compound products of the elected claims and the combination of said compound products and other components are related as combination-subcombination. Since they are related as combination-subcombination, the standard for requiring restriction herein is not met.

> In order to establish that combination and subcombination inventions are distinct, two-way distinctness must be demonstrated. To support a requirement for restriction, both two-way distinctness and reasons for insisting on restriction are necessary , i.e. separate classification, status, or field of search. See MPEP §808.02. If it can be shown that a combination, as claimed
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> (1) does not require the particulars of the subcombination as claimed for patentability (to show novelty and unobviousness), and
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> (2) the subcombination can be shown to have utility either by itself or in other and different relations, the inventions are distinct. When these factors cannot be shown, such

inventions are not distinct.
(Emphasis added.) (M.P.E.P. §806.05(c))

It is submitted that the first requirement for two-way distinctness is not established herein. The combination does require the particulars of the subcombination. The products of claims 12, 13, 14 and 31 all require the exact same compound products of the same scope as the subcombination claims of the elected group. To this end, the combination claims are even dependent upon the subcombination-product claims and the subcombination-products are an essential distinguishing feature of the combination-products.

It is respectfully submitted that when the relationship between the claimed subject matter is properly characterized, there is no basis for restriction herein. Thus, the restriction requirement should be withdrawn with regard to these product claims 12, 13, 14 and 31 at least.

Additionally, applicants bring the attention of the Examiner to MPEP § 821.04, Rejoinder, which states that "if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims [both process of making and using] which either depend from or include all the limitations of the allowable product will be rejoined." If the restriction requirement is maintained at this point regarding the withdrawn process and method claims (which are all dependent on the elected claims), the rejoinder of these non-elected claims is respectfully requested at the proper time in accord with the rejoinder provisions of the MPEP.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Csaba Henter/

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